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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,526	06/19/2001	David Meeker	4274-4000	2532

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/884,526	Applicant(s) Meeker et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 5, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) *2, 3, and 7-11* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 4-6* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of group II, claims 1 and 4-6, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MEP. § 818.03(a)).

2. Claims 2, 3 and 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 8.

Claims 1-11 are pending and claims 1 and 4-6 are under consideration. It should be noted that the elected invention, i.e. a method of combination therapy for treatment of a subject having Fabry disease comprising the combination of gene therapy and enzyme replacement therapy, is under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "administering a therapeutically effective amount of a combination therapy" in claim 1 is vague and renders the claim indefinite. It is unclear how to measure "a combination therapy" in therapeutically effective amount. It is unclear what material is being measured and provided in therapeutically effective amount. Claims 4-6 depend on claim 1 but fail to clarify the indefiniteness.

5. Claims 1 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: what is being administered in the combination therapy of gene therapy and enzyme replacement therapy and whether said combination therapy ameliorates the symptoms of Fabry disease.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 4-6 are directed to a method of combination therapy for treatment of a subject having Fabry disease comprising the combination of gene therapy and enzyme replacement therapy. Claim 5 specifies the combination therapy produces a diminution in globotriaosylceramide (GB3). Claim 6 specifies the enzyme replacement therapy provides an effective amount of α-galactosidase A.

The specification discloses general methods for gene therapy using adenoviral vectors, retroviral vectors, and non-viral vectors, and the reduction of GB3 by using small molecules, such as D-t-et-P4 and AMP-DNJ, following the GB3 reduction by α-galactosidase A enzyme replacement therapy. The claims encompass treating Fabry disease by combination therapy of gene therapy and enzyme replacement therapy comprising using any gene for gene therapy and any protein for enzyme replacement therapy.

The specification fails to provide adequate guidance and evidence for how to use any gene for gene therapy in combination with any protein for enzyme replacement therapy to treat Fabry disease in a patient via various administration routes so as to provide therapeutic effects for the Fabry disease *in vivo*.

The claims read on gene therapy and enzyme replacement therapy by using any gene in a vector in combination with any enzyme to treat Fabry disease via various administration routes *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings

available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene transfer (e.g. bridging pages 81-82). Similarly, the administration route of the protein or enzyme, the amount of the protein or enzyme that reach the target cells, the stability of said protein or enzyme within the cells or during the process of administration, and

the protein's compartmentalization within the cell are all important factors for a successful enzyme replacement therapy. In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

There is no evidence of record that administration of any gene, including DNA encoding α-galactosidase A, in a vector for gene therapy or any protein or enzyme, including α-galactosidase A, for enzyme replacement therapy or both to a patient having Fabry disease via various administration routes can ameliorate symptoms of said Fabry disease *in vivo*. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use any gene, including DNA encoding α-galactosidase A, in a vector for gene therapy in combination with any protein or enzyme, including α-galactosidase A, for enzyme replacement therapy to treat Fabry disease in a patient so as to provide therapeutic effects *in vivo* via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medin et al., 1996 (PNAS, Vol. 93, pp. 7917-7922) in view of Ioannou et al., 1996 (American Journal of Human Genetics, Vol. 59, No. 4, Suppl, pp. A15).

Claims 1 and 4-6 are directed to a method of combination therapy for treatment of a subject having Fabry disease comprising the combination of gene therapy and enzyme replacement therapy. Claim 5 specifies the combination therapy produces a diminution in globotriaosylceramide (GB3). Claim 6 specifies the enzyme replacement therapy provides an effective amount of α-galactosidase A.

Medin teaches construction of a recombinant retroviral vector expressing a human α-galactosidase A and correction of the enzymatic defect in multiple types of cells obtained from patients with Fabry disease by using said recombinant retroviral vector. Medin further teaches uptake of the secreted α-galactosidase A from the transduced cells by uncorrected cells and suggests that "endogenous metabolic correction in transduced cells, combined with secretion, may provide a continuous souse of corrective material in trans to unmodified patient bystander cells (e.g. abstract, discussion).

Medin does not teach combination of gene therapy with enzyme replacement therapy.

Ioannou teaches enzyme replacement therapy of Fabry disease in α-galactosidase A deficient mice by using α-galactosidase A protein and shows reduction of globotriaosylceramide in the treated α-galactosidase A deficient mice.

It would have been obvious for one of ordinary skill at the time of the invention to combine gene therapy and enzyme replacement therapy for treating Fabry disease by using a recombinant retroviral vector expressing α-galactosidase A as taught by Medin and a α-galactosidase A protein as taught by Ioannou because Medin teaches uptake of the secreted α-galactosidase A from the transduced cells by uncorrected cells and suggests that "endogenous metabolic correction in transduced cells, combined with secretion, may provide a continuous souse of corrective material in trans to unmodified patient bystander cells".

One ordinary skill at the time the invention was made would have been motivated to do so in order to correct the enzymatic defect in multiple types of cells obtained from patients with

Fabry disease as taught by Medin and to reduce globotriaosylceramide in α-galactosidase A deficient mice having Fabry disease by enzyme replacement therapy using α-galactosidase A protein as taught by Ioannou with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.